

**REMARKS**

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks presented herein, which place the application into condition for allowance.

**I. Status Of Claims And Formal Matters**

Claims 69-105, 126-128, 145, 156, 162-202 were pending in this application. Claims 1-73, 106-125, 129-144, 146-155 and 157-161 were withdrawn from consideration. Claims 1-68, 106-125, 129-144, 146-155, 157-161 have been cancelled. Claims 145 and 156 were placed in dependent form with respect to cancelled claims 144 and 150, respectively, as suggested by the Office Action. Claims 74, 80, 91, 99, 126, 127, 145, 171, 172, 173, 174, 175, 182, 183, 184, 185, 186, 187, 188, 189, 190, 192, 193, 194, 195, 196, 197, 198, 199, and 200 have been amended. Support for the amendments can be found throughout the specification, figures, and original claims. Accordingly, claims 69-105, 126-128, 145, 156, and 162-202 are now pending in this application.

It is respectfully asserted that no new matter is added by these amendments.

The Examiner is respectfully requested to consider and make of record U.S. Patent No. 6,766,817, issued to da Silva et al., entitled "Fluid Conduction Utilizing a Reversible Unsaturated Siphon with Tubarc Porosity Action," which is also cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449.

The Examiner has alleged that the current pending claims are not entitled to benefit of the priority date of October 31, 2002 of provisional application 60/422,755. The Office Action asserts that the present application claims a method of detecting WNV infection by testing for NS5 protein, and that the NS5 protein is not disclosed in 60/422,755. Applicants maintain the position that the priority date of the present claims should be October 31, 2002, not June 6, 2003. NS5 is mentioned on page 4 of the specification of provisional application 60/422,755. Furthermore, there are a number of instances throughout the specification wherein viral proteins are referred to, clearly including NS5. For example, on page 24, the specification states, "In another embodiment of this invention, the WNV polypeptides described herein are prepared as part of a larger fusion protein. For example, a WNV polypeptide used in a composition of this invention may be fused at its N-terminus or C-terminus to a *different immunogenic WNV polypeptide*, to a non-WNV polypeptide or to combinations thereof, to produce fusion proteins

comprising the WNV polypeptide.” Furthermore, “polypeptide” as defined on page 18 clearly encompasses NS5.

It is submitted that the claims are patentably distinct over the prior art and that these claim are and were in full compliance with the requirements of 35 USC §112. The amendments of the claims herein are not made for the purpose of patentability within the meaning of 35 USC §§ 101, 102, 103 or 112; but rather, the amendments are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the amendments should not give rise to any estoppel, as they are not narrowing amendments.

Any reference made herein to the present application is with respect to Paragraph Nos. of the published version of this application, namely US Publication No. 2004/0197769, which published October 7, 2004.

## **II. The Rejections Under 35 U.S.C. §112, Second Paragraph, Are Overcome**

The Office Action rejects claims 74, 80, 91, 99, 126-127, 145, 171-175, 182-190, 192-200 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The rejections to the above claims are based on several different grounds and are individually traversed as follows.

Claims 126-127, and 145 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite in the terminology “rapidly detecting” and “recent infection.” Applicants respectfully disagree with this rejection. However, in the interest of moving prosecution forward, Applicants have amended claims 126 and 145 to recite “rapid detection of” instead of “rapidly detecting.” Furthermore, Applicants have amended claim 145 to eliminate “recent” in terms of detecting a WNV infection. These amendments obviate the rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 74, 80, 91, 99, and 126 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the term “not substantially or detectably cross-reactive” fails to define if the anti-WNV antibodies are reactive or not reactive with antibodies against JEV, SLEV or DENV. Applicants respectfully disagree with this rejection. However, in the interest of moving prosecution forward, Applicants have amended claims 74, 80, 91, 99, and 126 to eliminate the term “but not substantially cross-

reactive with antibodies against JEV, SLEV, or DENV". The cancellation renders the rejection moot. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 171-175, 182-190, and 192-200 are rejected under U.S.C. §112, second paragraph, as being indefinite in the terminology "rapidly detecting" and "recent". Applicants respectfully disagree with this rejection. However, in the interest of moving prosecution forward, Applicants have amended claims 171-175, 182-190, and 192-200 to recite "the rapid detection of" rather than "rapidly detecting". Furthermore, Applicants have amended claims 193-200 to eliminate the term "recent or ongoing". These amendments obviate the rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 163, 168, 177 and 202 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims use the phrase "in less than about 3 hours." The Office Action asserts that the term "about" is relative and fails to particularly point the time the method is performed. The term "in less than" combined with "about" allegedly makes the time frame from this method indefinite. Applicants respectfully disagree.

One of ordinary skill in the art would be able to ascertain and appreciate the meanings of "less than about 3 hours" in reference to a method. Applicants would like to first point out that one can find other examples of patented claims that contain the recitation "about" in reference to time. For example, U.S. Patent No. 7,060,835 recites "[t]he process of claim 10 wherein the slurry is heated for a period of about 30 minutes to ***about 3 hours.***" And U.S. Patent No. 7,060,103 "[t]he method of claim 15 wherein said heat welding is accomplished for a time from ***about 7 minutes to about 24 hours.***" Applicants wish to make it clear that reference to the above patents does not necessarily bind them to any information contained therein, but rather is made for the purpose simply to demonstrate that, by patenting the claims the U.S.P.T.O. has taken the position that the recitation "less than about" in reference to time is not indefinite and its meaning can be understood by one of ordinary skill in the art. On the basis of these prior patents, reconsideration and withdrawal of the above rejection is respectfully requested. Moreover, MPEP 707.07(g) states in part that "[c]ertain technical rejections (e.g. negative limitations, indefiniteness) should not be made where the examiner, recognizing the limitations of the English language, is not aware of an improved mode of definition." It is presumed that the Examiner is aware of the effects of *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*

on patent prosecution, *i.e.* any amendment related to patentability can be viewed as prosecution history estoppel. In this environment, Applicants' representative cannot in good faith modify the claims on behalf of their clients if there are no reasons of record to support the rejection. Even if the applicants were amenable to modifying the claim, they cannot afford to guess at what the examiner would find to be permissible terminology. With this in mind, section 2173.02 of the MPEP is reproduced below:

The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, *not whether more suitable language or modes of expression are available*. When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. *Examiners are encouraged to suggest claim language to applicants to improve clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement.* (see MPEP 2173.02) (emphasis added)

Here, the term “less than about” defines the claimed subject matter with a “reasonable degree of particularity and distinctness.” One of ordinary skill in the art would appreciate the meaning of such terms based on their ordinary meanings and in context of the specification as a whole. Thus, “[s]ome latitude in the manner of expression and aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.” Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

### **III. The Rejections Under 35 U.S.C. §103 Are Overcome**

Claims 74, 76-105, 126-128, 145, 156, and 162-202 are rejected under 35 USC §103(a) as allegedly being obvious over Wang et al. (“Wang”), Valdes et al. (“Valdes”), Mandy et al (“Mandy”), Scaramozzino et al (“Scaramozzino”), and McDonell et al (“McDonell”).

The Office Action asserts that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teaching of Wang, Valdes and Mandy to use WNV NS5 protein to detect WNV infections in humans and horses. Further, that a person of ordinary skill in the art would have been motivated to use the NS5 and E proteins as

immunodiagnostic assays for the detection of WNV in biological samples. And, that McDonell teaches a diagnostic kit with an immunogenic composition using ELISA and fluorescent labeling. The Office Action further contends that one would have expected success because of the teachings of Scaramoizzino who developed a rapid, sensitive PCR assay for the detection of flavivirus with NS5 gene sequences.

To establish a *prima facie* case of obviousness, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. There must also be a reasonable expectation of success. Further still, the prior art reference alone or in combination must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants respectfully submit that the claims under rejection are not *prima facie* obvious over Wang, Valdes, Mandy, Scaramozzino, and McDonell since, *inter alia*, there lacks any motivation or suggestion to combine the references. Further, it is respectfully submitted that neither the references themselves nor the knowledge of persons of ordinary skill in the art provide any motivation or suggestion to combine the references.

Arguments from our previous response, filed March 17, 2005 remain relevant. Therein, Applicants reviewed the contrast between the present invention and the prior art at the time the instant application was filed. Specifically, Applicants responded to assertions that the claims of the present invention were *prima facie* obvious over Wang in view of Valdes and further in view of Mandy. In response, the present Office Action asserts that the claimed invention is obvious under 35 U.S.C. §103(a) in view of the combination of Wang, Valdes, Mandy, McDonell, and Scaramoizzino.

Initially, Applicants would like to point out that Applicants previously submitted a Declaration pursuant to 37 C.F.R. § 1.132 (hereinafter “Declaration”) stating that Wang is not the work of others as defined by 35 USC §102(a). Applicants re-attach the Declaration for Examiner’s convenience. Applicants respectfully assert that the Declaration is sufficient to overcome the grounds of rejection of claims 74, 76-105, 126-128, 145, 156, and 162-202 as obvious Wang, Valdes, Mandy, McDonell, and Scaramoizzino because the Declaration clearly states that T. Wang, L.A. Magnarelli, J.F. Anderson, L.H. Gould, S.L. Bushmich, and E. Fikrig did not make an independent inventive contribution to the invention claimed in this application. Therefore, it is respectfully submitted that Wang is not prior art.

Assuming arguendo that Wang could be considered prior art, Applicants assert that it does not make the present invention obvious. Wang relates to a method of detecting a WNV infection in an animal. More in particular, this reference relates to the preparation of and testing of recombinant forms of WNV E, M and NS1 antigens against sera obtained from horses known to be infected with WNV. The reference utilizes immunoblots to assess the performance of each of the antigens in the serodiagnosis of WNV infections. As Applicants previously argued, Wang reports that the WNV E protein is immunodominant and that “[a]ntibodies to the M protein or NS1 protein were not detected by immunoblot in all 10 West Nile virus-infected horses or six humans with West Nile virus.” (See page 107 of Wang). Thus, although the WNV E protein detected WNV-infected horse and human sera, neither M or NS1 detected any sera. Given Wang’s data that WNV E was “immunodominant” against the tested sera while WNV M nor NS1 were non-reactive, and given that nonstructural proteins (like NS1 or NS5) would generally be regarded by the ordinarily skilled person as less immunogenic than a viral structural protein (like E), Wang would not be suggestive to the skilled artisan that NS5, another nonstructural protein, would likely be a good candidate to detect a WNV infection with specificity and without substantial cross-reactivity to other flaviruses, especially JEV, DENV, and SLEV. Thus, Wang would in fact teach away from the present invention. Thus, the combination of this reference with Valdes, Mandy, Scaramozzino, and McDonell would not be proper.

Valdes relates to a method of characterizing the immune response to **DENV** structural and nonstructural proteins. In particular, Valdes tests sera from DENV fever patients and DENV hemorrhagic fever patients against DENV-2 and DENV-4 antigens E, NS1, NS3, and NS5 using Western blotting procedures. Therefore, this references relates to an entirely different virus than the present invention. As Applicants argued previously, In light of Wang which shows that a nonstructural protein is a poor antigen to use to detect WNV-infected sera, and in view of the fact that Valdes relates to an entirely different virus, namely DENV, at best, it would have been “obvious to try” combining the references. The Examiner, however, is reminded that “obvious to try” is not the standard under 35 USC §103. *In re Fine*, 5 USPQ 2d 1596, 1599 (Fed. Cir. 1988). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. See MPEP 2143.01. It is respectfully submitted that neither Wang nor Valdes provides the requisite suggestion or desirability to be combined to reach each and every element of the invention.

Further, to establish *prima facie* obviousness of a claimed invention, each of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974); also MPEP 2143.03. It is respectfully submitted that neither Wang nor Valdes, either alone or in combination, teaches nor suggests each and every element of claimed invention. For example, neither reference teaches or suggests a method for detecting a WNV infection in a subject by contacting a biological sample with a substantially purified NS5 protein or an immunogenic fragment thereof having a native conformation or non-denatured structure whereby the NS5 protein is specifically reactive with anti-WNV antibodies but not substantially cross reactive with antibodies against JEV, SLEV, or DENV. For example, Wang relates to the use of WNV E protein to detect a WNV infection, whereas the present invention relates, *inter alia*, to the use of WNV NS5 in a method to detect a WNV infection. And, surely Wang does not teach a WNV NS5 that has a native conformation or non-denatured structure and that is specifically cross-reactive with anti-WNV antibodies but not substantially cross reactive with other flaviviruses, especially JEV, SLEV, and DENV.

Valdes relates to analyzing the antibody response to DENV infected sera, including the response to DENV E, NS1, NS3, and NS5 antigens. Contrary to Valdes, the instantly claimed invention relates to detecting WNV infections, not DENV infections. Although DENV and WNV are related flaviviruses, it would not have been obvious to extend the results of Valdes to modify, especially in view of the inconsistent data and lack of data presented in Valdes. For example, the reactivity of NS3 from DENV-2 and DENV-4 is completely different and NS5 is tested for only a single DENV type (see Table 1). Valdes does not correct for the deficiencies in Wang, and vice versa. Neither Wang nor Valdes, either alone or in combination, teach a method for the detection of a WNV infection in a subject suspected of having said infection that includes the step of contacting a biological sample from the subject with an isolated and substantially purified polypeptide comprising a WNV NS5 protein having a native conformation or non-denatured structure whereby the NS5 protein or the immunogenic fragment thereof is specifically reactive with anti-WNV antibodies but not substantially cross-reactive with antibodies against JEV, SLEV, or DENV.

Moreover, because Valdes relates to DENV, and not WNV, Applicants point out that the differences in the method of transmission between the viruses is relevant. In particular, because humans are amplifying hosts for dengue viruses, the patients have high levels in the blood for

long enough time that mosquitoes can transmit the virus to other humans through biting an infected individual. The situation with WNV, however, is different. Humans are not amplifying hosts and the viral load in a human infected with WNV is so low that mosquitoes cannot transmit WNV from one infected human to another. This difference is important, because one skilled in the art would have no motive to postulate that NS5 of WNV would have been a good diagnostic antigen since there was not reason to presuppose that with low viremia, infected humans would have had a strong immune response, i.e., generating antibodies against WNV NS5. Accordingly, the combination of this reference with Wang, Mandy, Scaramozzino, and McDonell would not be proper.

Mandy relates to an immunoassay that makes use of a new technology, suspension array technology (SAT). SAT involves using flow cytometry to make quantitative measurements, using microfluorospheres as solid support (coated with protein) and antibodies as reporter molecules. The reference is concerned with describing critical aspects and limitations of SAT. Contrary to the contention in the Office Action that “Mandy teaches that antibodies that are used in ELISA assays can predictably be used in SAT assays”, this reference notes that SAT use as an immunoassay was, at the time of publication, essentially still in a developmental stage, including commercial availability of kits (page 714, 720, and 723); that “the impact of multiplexed assays has been limited to date” (page 720); that the “...implementation of SAT for biomedical research is *anticipated*” (page 720); and that cytokine panels are representative of immunoassays that are most likely to gain wide application and possible acceptance, for monitoring drug and vaccine trials against various infectious agents (page 720). Furthermore, Mandy only generically refers to SAT, such as multiplex assays on Luminex. Although it discusses *potential*, it fails to demonstrate that SAT is an effective diagnostic tool for any flavivirus infection, and certainly not for WNV in particular. On the contrary, the present invention demonstrated the use of SAT in differentiating WNV infection from either infection or vaccination with other flaviviruses. Accordingly, the combination of this reference with Wang, Valdes, Scaramozzino, and McDonell would not be proper.

Scaramozzino relates to the design of new primers allowing heminested PCR involving the alignment of NS5 gene sequences of 30 different flaviviruses. The reference relates to a *genus* PCR procedure that might serve as a first-line diagnostic PCR screening test for an unknown virus. The procedure would not ensure a definitive phylogenetic analysis. Although

this initial procedure may take only a few hours, a definitive identification to the pathogenic members of the genus Flavivirus would require *further* complete sequencing or cell culture.

Moreover, Scaramozzino is a molecular amplification test, which is only capable of detecting and measuring a virus if it is still present in the host. On the other hand, while the present invention is able to detect a current infection, it is also useful as a diagnostic for *prior* infection of a flavivirus. Scaramozzino provided no incentive or motivation to use NS5 as an antigen for antibody protection. In particular, Scaramozzino did not teach or suggest that NS5 would be a successful antigen for antibody detection. In essence, the use of a sequence in a PCR procedure cannot be said to predict the effectiveness of the structural protein derived from that sequence in an immunological procedure. Accordingly, the combination of this reference with Wang, Valdes, Mandy, and McDonell would not be proper.

McDonell involves a recombinant *NS1/E* composition, although the reference suggests that other NS proteins may replace NS1. The reference discusses the potential usefulness of the composition as a vaccine and in immunoassays. However, McDonell only relates to NS1 and DENV infections. Although DENV and WNV are related flaviviruses, it would not have been obvious to extend the results of McDonell to arrive at the present invention, especially in view of the unpredictability of immune responses to antigenic proteins from different viruses. Accordingly, the combination of this reference with Wang, Valdes, Mandy, and Scaramozzino would not be proper.

Neither Wang, Valdes, Mandy, Scaramozzino, nor McDonell either alone or in combination, teach a method for the detection of a WNV infection in a subject suspected of having said infection that includes the step of contacting a biological sample from the subject with an isolated and substantially purified polypeptide comprising a WNV NS5 protein having a native conformation or non-denatured structure whereby the NS5 protein or the immunogenic fragment thereof is specifically reactive with anti-WNV antibodies but not substantially cross-reactive with antibodies against JEV, SLEV, or DENV.

Accordingly, in view of the preceding comments, reconsideration and withdrawal of the 35 USC §103 rejection in view of Wang, Valdes, Mandy, Scaramozzino, nor McDonell is respectfully requested.

**IV. Double Patenting Is Held In Abeyance**

The Office Action provisionally rejects claims 74-105, 126-128, 145 and 156, and 162-202 under judicially created doctrine of double patenting over claims 1-9, 13-21, 24-35 and 56-57 of copending Application No. 10/839,442.

The issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

**REQUEST FOR INTERVIEW**

If any issue remains as an impediment to allowance, an interview with the Examiner is respectfully requested, prior to issuance of any paper other than a Notice of Allowance; and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

**CONCLUSION**

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application, reconsideration and withdrawal of the rejections of and objections to the application, and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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